Imaging Regional Alterations of Gas Exchange in a Murine Model of Emphysema

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INTRODUCTION: Pulmonary imaging with hyperpolarized (HP) ^{3}He MRI is a sensitive probe for lung microstructure and function. Emphysema, a primary subcategory of COPD, is characterized by abnormal enlargement of lung components from the distal to the terminal bronchioles. It is accompanied by alveolar wall destruction and tissue density loss. In this work, we use HP ^{3}He MRI measurements of alveolar partial pressure of oxygen (P_AO_2), apparent diffusion coefficient (ADC), and fractional ventilation (r) in conjunction with localized histological analysis to assess the changes in lung function and structure in an elastase-induced murine model of emphysema. Measurements of P_AO_2 and r are directly related to alveolar gas exchange and gas replacement respectively, and can further our basic understanding of the underlying mechanisms of emphysema onset and progression**.**

METHODS: A group of male BALB/c mice (n=6) were divided into two equal-numbered cohorts: (1) healthy controls (2) elastase-induced. Emphysema was induced through a single intratracheal instillation of 22U/100g of porcine pancreatic elastase, and animals were studied approximately 3 months after the model induction. Animals were sedated with 100mg/kg intraperitoneal ketamine and 10 mg/kg xylazine. Treacheotomy was performed with a 1.5-mm ET tube. Saturation level of blood oxygen and heart rate were monitored using an MR-compatible rodent pulseoximeter (Nonin Medical, Inc., Plymouth, MN). Mice were mechanically ventilated with a tidal volume of 1.2ml/100g body weight at 110 BPM and I:E=1:2 with breathing air. During imaging, the ventilation was switched from air to a mixture of ^{3}He:O_2 (4:1) with identical ventilation parameters. Imaging was performed on a 50-cm 4.7-T MRI scanner equipped with 12-cm 25G/cm gradients. The mice were placed supine in the magnet and a 1"-diameter surface coil tuned to 152.95 MHz was placed on top of the chest, while the animal was positioned supine in the magnet. For the ventilation and P_AO_2 measurements, multi-slice coronal images were acquired using a fast gradient echo pulse sequence with FOV=3×3cm^2, matrix size=64×64, THK=4mm, α=15° (r and P_AO_2) and 40° (ADC), MS=64×64 pixels (planar resolution of ~470 µm). Fractional ventilation r, ADC, and P_AO_2 were imaged as described earlier [1, 2]. ADC images were obtained using a diffusion-weighted gradient echo imaging pulse sequence with Δ=1 ms, and b-values = 0.0 and 2.18 s/cm^2 along the phase encoding direction. Pulse width calibration was performed on the loaded RF coil to estimate the applied flip angle for each animal. Separately, whole slice histomorphologic analysis was performed on all the animals.

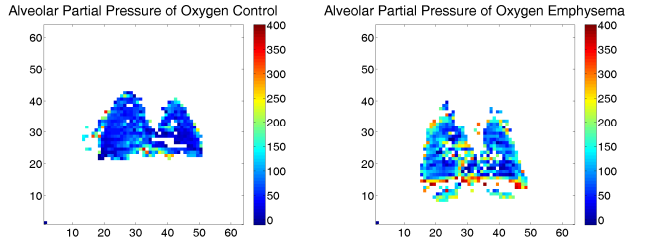

Figure 1. Representative maps of alveolar partial pressure of oxygen of control and emphysematous mouse.

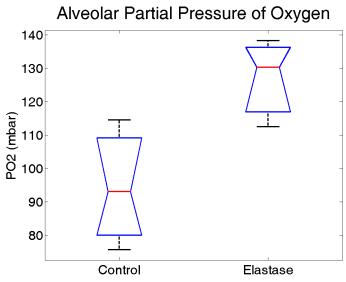

Figure 2. Mean and SD of P_AO_2 in control and emphysematous group.

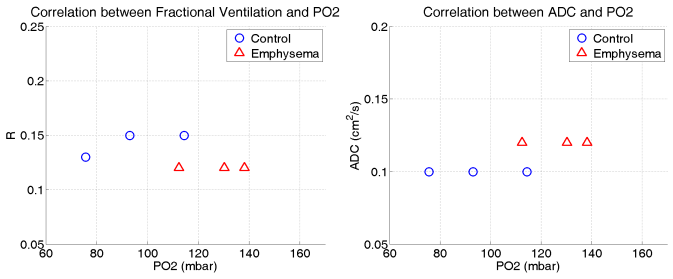

Figure 3. Left plot: Correlation between P_AO_2 and ADC
Right plot: Correlation between P_AO_2 and Fractional Ventilation.

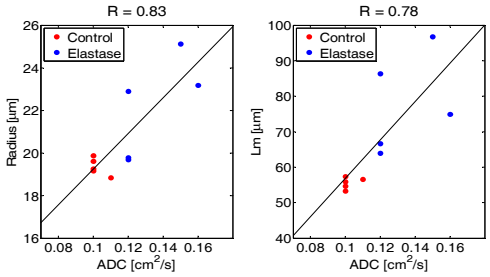

Figure 4. Left curve: Correlations between mean alveoli radius and ADC.
Right curve: Correlations between L_m and ADC.

RESULTS: Figure 1 shows representative maps of P_AO_2 in control and emphysematous animals. **Figure 2** shows P_AO_2 mean and standard deviation for the two groups showing that the healthy group has a smaller P_AO_2 value of 94.37±19.44 mbar compared to the elastase group at 126.99±13.19 mbar (the difference is not quite statistically significant with p = 0.074, which is most likely a result of the small sample size in this study and will be addressed as the study progresses), but it shows the difference on a scale of the average values of the two groups. **Figure 3** shows the correlation between P_AO_2 and ADC, as well as fractional ventilation. It can be seen that the P_AO_2 measurements can differentiate animals that appear the same under both ADC and ventilation metrics. Although the mean ADC of elastase-induced mice is higher than that of healthy animals, P_AO_2 shows a larger difference between the two groups. In agreement with a lower mean r in emphysematous mice compared to healthy mice, the higher mean P_AO_2 values show a compromised O_2 uptake through the alveolar membrane, most likely due to destruction of alveolar walls and loss of elastic recoil. **Figure 4** shows the correlations between the histological indices (mean alveoli radius and L_m) and ADC values indicating effective elastase model induction.

CONCLUSION: Our preliminary results show a non-negligible change in alveolar partial pressure of oxygen between controlled and elastase-induced mice, indicating that P_AO_2 imaging by HP ^{3}He MRI can be a sensitive tool to investigate lung disease models, specifically those affecting the membrane function. The higher value of the mean linear intercept and ADC represent tissue destruction in the elastase-induced animal, which are concurrent with the compromised O_2 uptake efficiency in these animals as evidenced by an elevated P_AO_2 and a declined fractional ventilation measurements.

REFERENCES: [1] Emami *et al.*, Mag Reson Med. (2010). [2] Kadlecek *et al.*, Proc Intl Soc Mag Reson Med. (2009).